26. (New) An article of manufacture comprising packaging material and a cloning system for generating recombinant adenovirus comprising:

(a) an Ad backbone plasmid comprising an Ad genome lacking map units 0 to 9.2, wherein the numbering of the map units starts with the lefthand ITR and wherein the backbone plasmid lacks a loxP sequence, and

(b) a shuttle plasmid comprising Ad sequences from 0 to 1 and 9.2 to 16.1 map units of an Ad genome, wherein the shuttle plasmid lacks a loxP sequence,

wherein said packaging material comprises instructions that indicate that the cloning system can be used for generating recombinant adenovirus.

REMARKS

Applicant has carefully reviewed and considered the Office Action mailed on November 16, 2000, and the references cited therewith.

Claims 2-8, 10, 11, 16, 17, and 22 are amended, claims 1 and 9 are canceled, and claim 26 is added; as a result, claims 2-8 and 10-26 are now pending in this application. No new subject matter has been added. The amendments are made to clarify the claims, and not for reasons relating to patentability. Therefore, the amendments are not intended to limit the scope of equivalents to which any claim element may be entitled.

The amendments to the claims are fully supported by the specification as originally filed. Concerning the amendments to claims 16, 17 and 22 regarding the numbering of the map units, the specification, for example, at page 6, lines 21-23 indicates that map units 0 to 9.2 of the genome have been deleted, starting with the left-hand ITR. These amendments are made simply to clarify the numbering scheme and are not related to patentability.

Regarding the recitation that the plasmid lacks a loxP sequence in claims11,6, 17 and 22, one having ordinary skill in the art upon reading the full disclosure would recognize that a loxP sequence is not a part of the present invention because the specification does not discuss a Cre-lox recombination system, except when discussing the prior art. Adequate description under the first paragraph of 35 U.S.C. §112 does not require literal support for the claimed invention. Rather, it is sufficient if the originally-filed disclosure would have conveyed to one having ordinary skill in the art that an appellant had possession of the concept of what is claimed. These amendments are made simply to clarify the content of the plasmids and are not related to patentability.

Claims 2-8 and 10 have been amended to depend from claim 16 due to claim 1 being cancelled. These amendments are made for reasons not related to patentability.

New claim 26 is supported, for example, at page 4, lines 7-9 and at page 6, line 26 through page 7, line 8. These amendments are made for reasons not related to patentability.

§112 Rejection of the Claims

Claims 1-10, 16, and 17-25 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

In particular, regarding pending claims 1, 16, 17 and 22, the Examiner requested clarification regarding the presence or absence of the ITR. Claims 16, 17 and 22 have been amended to clarify that the lefthand ITR is not present, i.e., that the lefthand ITR is contained in the deleted portion of the Ad genome. Claim 1 has been cancelled.

Regarding claim 9, the Examiner has asked for clarification of the positioning of the HSV Amplicon. Claim 9 has been deleted thereby rendering this rejection moot.

Applicant respectfully requests that the rejections under 35 U.S.C. § 112, second paragraph be withdrawn.

§102 Rejection of the Claims

Claims 1, 4-6, 10, 11, 13-19, and 22-25 were rejected under 35 U.S.C. § 102(b) as being anticipated by Aoki *et al.*, Molecular Medicine 5:224-231 (1999). This rejection is respectfully traversed.

A proper rejection under §102(b) requires that a cited reference identically describe or disclose all of the elements of the claimed invention. The present claimed invention is directed to Adenovirus backbone plasmids and cloning systems that lack a loxP sequence, and methods of using these cloning systems. The amendments to the claims clarify that the backbone plasmids of the present invention specifically lack loxP sequences, and therefore do not use a Cre-loxP recombination method.

Aoki *et al.*, in contrast, discuss an adenoviral vector that uses the Cre-loxP system. In particular, at page 225, they discuss constructing a shuttle plasmid that contains a loxP, and constructing an adenoviral cosmid containing a loxP site. A cell-free reaction mixture consisting of viral and plasmid DNAs and Cre recombinase was prepared, wherein Cre recombinase produces the full-length recombinant adenoviral vector in vitro by intermolecular recombination between the loxP sites in these tow linearized molecules. Aoki *et al.* at page 226, Results.

Applicant respectfully requests that the rejections under 35 U.S.C. § 102(b) be withdrawn because Aoki *et al.* does not identically describe or disclose all of the elements of the claimed invention.

§103 Rejection of the Claims

Claims 2, 3, 20 and 21

Claims 2, 3, 20 and 21 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Aoki *et al.* and further in view of Krougliak *et al.*(Human Gene Therapy 6:1575-1586, 1995), Breakfield *et al.*, (US Patent 5,965,441) and Charier *et al.* (J. Vir. 70:4805-4810, 1996).

Applicant respectfully submits that the present claims are not prima facie obvious over the cited references. To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the cited references themselves or in the knowledge generally available to an art worker, to modify the reference or to combine reference teachings so as to arrive at the claimed invention. Second, the art must provide a reasonable expectation of success. Finally, the prior art reference must teach or suggest all of the claim limitations. The teachings or suggestions, as well as the expectation of success, must come from the prior art, not applicant's disclosure.

As discussed above, the claims of the present invention recite a cloning system that uses adenoviral backbone vectors that lack a loxP sequence, whereas Aoki *et al.* discuss an adenovirus backbone (cosmid) vector that uses the Cre-loxP system. Therefore, Aoki *et al.* does not teach or suggest all of the claim limitations as required for obviousness.

Krougliak *et al.* does not remedy the deficiencies of Aoki *et al.* There is no suggestion or motivation, either in the cited references themselves or in the knowledge generally available to an art worker, to modify the references, or to combine the teachings of the references, so as to arrive at the claimed invention. Pending claims 2, 3, 20 and 21 recite a two-part cloning system; the first element being a backbone plasmid comprising map units 9.2 to 100 of an Ad genome (but lacking a loxP sequence), and the second element being a shuttle plasmid comprising 0 to 1 and 9.2 to 16.1 map units of an Ad genome (also lacking a loxP sequence). Krougliak *et al.* generated cell lines that could complement E1, E4 and protein IX defective adenovirus type 5 (Ad5) mutants. The plasmid system used by Krougliak *et al.* contained adenovirus sequences from the left ITR to the right ITR (i.e., the full viral backbone), except for sequences encoding E1, E4 or protein IX. The intention of the deletions by Krougliak *et al.* was to provide for more space to accommodate larger inserts placed into the E1 region of the adenovirus vector and not to otherwise modify the backbone. If one of skill in the art logically combined these two references

one would develop a full-length adenoviral vector (except that it lacks sequences encoding E1, E4 or protein IX) that uses the Cre-loxP system in a cell line that complements E1, E4 and protein IX defective Ad5 mutants. The present invention is distinguishable over such a system in that the cloning system of the present invention specifically lacks the lefthand ITR and loxP sequences in the backbone and shuttle plasmids.

Thus, neither of these references, either alone or taken in combination, teach the present claimed invention. Therefore, Applicant respectfully requests that this rejection under 35 U.S.C. § 103 be withdrawn.

Claims 7-9

Claims 7-9 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Aoki *et al.* and Krougliak *et al.* and further in view of Breakfield *et al.* (U.S. 5,965,441).

Claims 7-8 (claim 9 having been cancelled) have been amended to recite a two-plasmid cloning system where both the shuttle and backbone plasmids lack loxP sequences. As discussed above, this cloning system is distinguishable over Aoki *et al.* in view of Krougliak *et al.* because the backbone used in the present system lacks the lefthand ITR and loxP sequences.

Breakfield *et al.* does not remedy the shortcomings of Aoki *et al.* combined with Krougliak *et al.* Breakfield *et al.* teach a hybrid vector system that incorporate elements of herpesvirus and adeno-associated virus that is capable of expressing a gene product in eukaryotic cells. The Examiner admits that Breakfield *et al.* is deficient in that it does not teach an adenovirus vector. The Examiner states, however, that "one of ordinary skill in the art at the time was made would have been motivated to apply the AAV/HSV hybrid vector taught by Breakfield *et al.* to the fast method for generating recombinant Ad viruses without contamination of the wild type virus taught by Aoki *et al.* with the cell line that successfully produced recombinant adenoviruses that have large sections deleted from them taught by Krougliak *et al.*" Applicant respectfully reminds the Examiner, however, that the "fast method for generating recombinant Ad viruses" taught by Aoki *et al.* requires the use of Cre-loxP, which is different from the present invention. Therefore, if these three references are logically combined, one would have the Aoki *et al.* Ad vector containing a loxP sequence and the Breakfield *et al.* AAV/HSV hybrid sequences in the Krougliak *et al.* cell line (in a backbone containing the lefthand ITR). In contrast, the plasmids used in the present claimed cloning system do not contain loxP sequences or the lefthand ITR.

Therefore, Applicant respectfully requests that this rejection under 35 U.S.C. § 103 be withdrawn.

Claim 12

Claim 12 was rejected under 35 U.S.C. § 103(a) as being unpatentable over Aoki *et al.*, Krougliak *et al.*, and Breakfield *et al.* as applied to claims 1-11 and 13-25 above, and further in view of Chartier *et al.* Aoki *et al.*, Krougliak *et al.*, and Breakfield *et al.* are discussed above. Chartier *et al.* do not remedy the deficiencies of Aoki *et al.*, Krougliak *et al.*, and Breakfield *et al.* Chartier *et al.* disclose the introduction of unique PacI site into and Ad5 vector.

There is no suggestion or motivation in the cited references to combine the teachings of the references so as to arrive at the claimed invention. Claim 12 recites a shuttle plasmid comprising Ad sequences wherein PacI restriction endonuclease sites flank either end of the Ad sequences, but wherein the plasmid lacks a loxP sequence. If Aoki *et al.*, Krougliak *et al.*, Breakfield *et al.* and Chartier *et al.* are combined, one would have the Aoki *et al.* Ad vector containing a loxP sequence, the Breakfield *et al.* AAV/HSV hybrid sequences and the Chartier *et al.* PacI sites in the Krougliak *et al.* cell line (in a backbone containing the lefthand ITR). In contrast, the present claimed invention does not contain loxP sequences or the lefthand ITR. Therefore, Applicant respectfully requests that this rejection under 35 U.S.C. § 103 be withdrawn.

Conclusion

Applicant respectfully submits that the claims are in condition for allowance and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney (612-373-6961) to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

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CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail, in an envelope addressed to: Commissioner of Patents, Washington, D.C. 20231, on this 12 day of April, 2001.

Candis B. Buending
Name

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Signature